

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 10 APR 2006

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Applicant's or agent's file reference P036148WO HRG		<b>FOR FURTHER ACTION</b>		See Form PCT/PEA/416
International application No. PCT/IB2004/004335		International filing date (day/month/year) 06.12.2004		Priority date (day/month/year) 05.12.2003
International Patent Classification (IPC) or national classification and IPC INV. C07K14/705 G06F19/00				
Applicant UNIVERSITY OF GRONINGEN et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 7 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand  05.10.2005		Date of completion of this report  07.04.2006		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer  Petri, B  Telephone No. +49 89 2399-7356		



# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.  
PCT/IB2004/004335

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
    - ☐ international search (under Rules 12.3 and 23.1(b))
    - ☐ publication of the international application (under Rule 12.4)
    - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

### Description, Pages

1-56 as originally filed

### Sequence listings part of the description, Pages

1-4 received on 17.03.2005 with letter of 16.03.2005

### Claims, Numbers

1-56 received on 17.10.2005 with letter of 12.10.2005

### Drawings, Sheets

1/24-24/24 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
  - ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
  - ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/IB2004/004335

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	8, 10, 12-13, 15, 17, 28, 34, 41-53, 60-62
	No: Claims	1-7, 9, 11, 14, 16, 18-27, 33, 35-38, 54-59
Inventive step (IS)	Yes: Claims	8, 10, 12-13, 15, 17, 28, 34, 41-53, 60-62
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-62
	No: Claims	

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/IB2004/004335

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**Supplemental Box relating to Sequence Listing**

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**Continuation of Box I, item 2:**

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

a. type of material:

- ☒ a sequence listing
- ☒ table(s) related to the sequence listing

b. format of material:

- ☒ in written format
- ☒ in computer readable form

c. time of filing/furnishing:

- ☐ contained in the international application as filed
- ☐ filed together with the international application in computer readable form
- ☒ furnished subsequently to this Authority for the purposes of search and/or examination
- ☐ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

**Re Item I**

**Basis of the report**

Reference is made to the following documents:

- D1: WO 03/029420 A (GENENTECH, INC; KELLEY, ROBERT F; LINDSTROM, STEPHANIE H) 10 April 2003 (2003-04-10)
- D2: WO 99/36535 A (GENENTECH, INC; ASHKENAZI, AVI, J; KELLEY, ROBERT, F; O'CONNEL, MARK,) 22 July 1999 (1999-07-22)
- D3: WO 01/00832 A (GENENTECH, INC) 4 January 2001 (2001-01-04)
- D4: WO 88/06625 A (CETUS CORPORATION) 7 September 1988 (1988-09-07)
- D5: WO 2004/001009 A (GENENTECH, INC; HYMOWITZ, SARAH; KELLEY, ROBERT, F; LINDSTROM, STEPHAN) 31 December 2003 (2003-12-31)
- D6: VAN DER SLOOT ALMER M ET AL: "Stabilization of TRAIL, an all-beta-sheet multimeric protein, using computational redesign." PROTEIN ENGINEERING, DESIGN & SELECTION : PEDS. SEP 2004, vol. 17, no. 9, September 2004 (2004-09), pages 673-680, XP002324633 ISSN: 1741-0126

**Re Item II**

**Priority**

Since the priority document/s pertaining to the present application is/are not yet available to the IPEA, this Written Opinion/IPER has been drawn up considering the priority date as valid. D5 and D6 have/has been published between the priority date and the filing date of the present application. Thus, said documents are / document is not considered to constitute prior art in the meaning of rule 64(1)(b) PCT. However, if it turns out that the effective date of the claimed subject-matter is not the priority date then D5/D6 will become relevant to assess whether the present application satisfies the criteria set forth in Article 33(2) and (3) PCT.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

PCT/IB2004/004335

The instant application relates to muteins of TRAIL with desired properties (enhanced thermal stability and/or new receptor specificity). Claims are directed to positions 125, 163, 185, 187, 194, 196, 203, 205, 208, 225, 227, 230, 232, 234, 237, 239, 240, 241, 271, 272, 274, 280. Effects have been reported for E194I/I196S; D203/Q205M/Y237F; S225A; R227M; E194I/I196S/D203/Q205M/Y237F.

D1-D5 all disclose muteins for TRAIL/TNF at positions overlapping with the claimed positions. Claims 1-7, 9, 11, 14, 16, 18-27, 33, 35-38, 54-59 therefore lack novelty (Article 33(2) PCT).

The fact that certain effects/properties have not been examined for prior art products is irrelevant for assessing novelty for structurally indistinguishable products. Such properties have to be inherent. The same applies for products that may be produced by a novel process. This also applies for structural criteria as those of items a)-d). If a prior art document discloses a mutant TRAIL with a substitution at position that is also listed in e.g. claim 6, than it is irrelevant for the question of novelty whether claim one defines the positions with parameters other than a particular amino acid position.

The question on whether results to be achieved like definitions such as "so as to improve the free energy" "so as to be more stable" can serve as functional features to distinguish subject-matter for which protection is sought hinges on three prerequisites. (1) Does the application disclose a concept fit for generalisation that enables the skilled person to determine the nature of the substitutions over the entire breadth claimed that give the desired result? (2) Are test disclosed or known to the skilled person that allow to determine whether a given mutein has the desired properties? (3) Do the muteins of the prior art not have these desired properties? In said context it will be relevant that not all disclosed muteins have the desired properties (see below).

The same rational is to be applied to asses the allowableness of the unusual parameters a)-d) of claim 1.

**Re Item VIII**

**Certain observations on the international application**

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

PCT/IB2004/004335

Claims 1-7, 9, 11, 14, 16, 18-27, 33, 35-38, 54-59 relate to cytokine/TRAIL muteins defined only by reference to the result to be achieved (Article 6 PCT)(see also above).

The claim set encompasses 7 independent claims all directed to cytokine muteins, as such contravening the conciseness criterion (Article 6 PCT).

Apparently not all mutations at the indicated positions even for TRAIL result in the muteins with desired properties (see page 38 lines 23-28)(Article 5 PCT).

From the previous it appears as if only particular structurally defined muteins of TRAIL could form a basis for a reasonable set of claims. In particular muteins with clearly defined structural features and demonstrated technical effects such as those of claim 7, 9-10, 12 appear to be novel and inventive. The extend to what this particular teaching can be broadened largely depends on the criteria as set out in the previous paragraph.

The electronically filed sequence is different from the originally filed sequences at pages 55-56.

Subject-matter for which protection is sought is to be defined by technical features that are clear in itself not by reference to prior art documents (claim 3)(Article 6 PCT).